ClinicalEvidence

Dementia

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ABSTRACT

INTRODUCTION: Dementia is characterised by chronic, global, non-reversible deterioration in memory, executive function, and personality. Speech and motor function may also be impaired. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of treatments on cognitive symptoms of dementia (Alzheimer's, Lewy body, or vascular)? What are the effects of treatments on behavioural and psychological symptoms of dementia (Alzheimer's, Lewy body, or vascular)? We searched: Medline, Embase, The Cochrane Library, and other important databases up to April 2008 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 33 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review, we present information relating to the effectiveness and safety of the following interventions: acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine), antidepressants (clomipramine, fluoxetine, imipramine, sertraline), antipsychotics (haloperidol, olanzapine, quetiapine, risperidone), aromatherapy, benzodiazepines (diazepam, lorazepam), cognitive behavioural therapy (CBT), cognitive stimulation, exercise, ginkgo biloba, memantine, mood stabilisers (carbamazepine, sodium valproate/valproic acid), music therapy, non-steroidal anti-inflammatory drugs (NSAIDs), omega 3 (fish oil), reminiscence therapy, and statins.

QUESTIONS

INTERVENTIONS

COGNITIVE SYMPTOMS

Likely to be beneficial

Unknown effectiveness

Unlikely to be beneficial

BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS

Likely to be beneficial

Trade off between benefits and harms

Unknown effectiveness

Key points

- Dementia is characterised by chronic, global, non-reversible deterioration in memory, executive function, and personality. Speech and motor function may also be impaired.
- Median life expectancy for people with Alzheimer's and Lewy body dementia is about 6 years after diagnosis, although many people may live far longer.
- RCTs of dementia are often not representative of all people with dementia; most are 6 months or less, not in primary care, and most RCTs are in people with Alzheimer's disease. There are fewer RCTs in people with vascular dementia, and fewer still in people with Lewy body dementia.

- Cognitive symptoms of dementia can be improved by acetylcholinesterase inhibitors (donepezil, galantamine, and rivastigmine).

  Acetylcholinesterase inhibitors seem to improve cognitive function, global state, and activities of daily living scores compared with placebo at 26 weeks in people with Alzheimer's disease.

  However, they may be associated with an increase in adverse effects, particularly GI symptoms (anorexia, nausea, vomiting, or diarrhoea).

- We don't know whether cognitive stimulation, music therapy, reminiscence therapy, omega 3 fish oil, statins, or NSAIDs are effective at improving cognitive outcomes in people with cognitive symptoms of dementia, as we found insufficient evidence.

- In people with cognitive symptoms, memantine may improve global state and activities of daily living scores in people with moderate to severe Alzheimer's disease over 24 to 28 weeks, but we don't know about these in mild to moderate Alzheimer's disease.

  Although memantine is associated with a statistically significant increase in cognition scores in some population groups, the clinical importance of these results is unclear.

- Ginkgo biloba is unlikely to improve cognitive function in people with Alzheimer's disease or vascular dementia. However, evidence is of poor quality so this conclusion should be interpreted with caution.

- Acetylcholinesterase inhibitors may marginally improve neuropsychiatric symptoms compared with placebo in people with behavioural and psychological symptoms of dementia, but they are also associated with adverse effects.

- Antidepressants (clomipramine, fluoxetine, imipramine, sertraline) may improve depressive symptoms compared with placebo in people with Alzheimer's disease associated with depression.

  However, RCTs were small and short term, and adverse effects were sparsely reported.

- Memantine may be associated with a small improvement in neuropsychiatric symptoms compared with placebo in people with behavioural and psychological symptoms of dementia, but it is also associated with adverse effects.

- We don't know whether diazepam, lorazepam, aromatherapy, CBT, exercise, carbamazepine, or sodium valproate/valproic acid are effective at improving neuropsychiatric symptoms in people with behavioural and psychological symptoms of dementia, as we found insufficient evidence.

- Some antipsychotics may improve neuropsychiatric symptoms or aggression in people with behavioural and psychological symptoms of dementia, but antipsychotics are also associated with an increase risk of severe adverse events such as stroke, TIA, or death.

- CAUTION: Regulatory bodies have issued alerts that both conventional and atypical antipsychotics are associated with an increased risk of death in elderly people treated for dementia-related psychosis.

DEFINITION

Dementia is characterised by memory loss (initially of recent events), loss of executive function (such as the ability to make decisions or sequence complex tasks), other cognitive deficits, and changes in personality. This decline must be serious enough to affect social or occupational functioning, and reasonable attempts must be made to exclude other common conditions, such as depression and delirium. **Alzheimer's disease** is a type of dementia characterised by an insidious onset and slow deterioration, and involves impairments in memory, speech, personality, and executive function. It should be diagnosed after other systemic, psychiatric, and neurological causes of dementia have been excluded clinically and by laboratory investigation. **Vascular dementia** is often due to multiple large or small vessel disease. It often presents with a stepwise deterioration in cognitive function with or without language and motor dysfunction. It usually occurs in the presence of vascular risk factors (diabetes, hypertension, arteriosclerosis, and smoking). Characteristically, it has a more sudden onset and stepwise progression than Alzheimer's disease, and often has a patchy picture of cognitive deficits. **Lewy body dementia** is a type of dementia that involves insidious impairment of cognitive function with parkinsonism, visual hallucinations, and fluctuating cognitive abilities. Night time disturbance is common and there is an increased risk of falls. [1] [2] Careful clinical examination of people with mild to moderate dementia and the use of established diagnostic criteria accurately identifies 70% to 90% of causes confirmed at post mortem. [3] [4] In all types of dementia, people will experience problems with cognitive functioning and are likely to experience behavioural and psychological symptoms of dementia. Where possible, we have divided outcomes into cognitive or behavioural/psychological, although there is often considerable crossover between these outcomes, both clinically and in research. This review deals solely with people with Alzheimer's disease, Lewy body dementia, or vascular dementia.

INCIDENCE/ PREVALENCE

About 6% of people aged over 65 years and 30% of people aged over 90 years have some form of dementia. [5] Dementia is rare before the age of 60 years. Alzheimer's disease and vascular dementia (including mixed dementia) are each estimated to account for 35% to 50% of dementia, and Lewy body dementia is estimated to account for up to 5% of dementia in the elderly, varying with geographical, cultural, and racial factors. [1] [5] [6] [7] [8] [9] There are numerous other causes of dementia, all of which are relatively rare, including frontotemporal dementia, alcohol-re-

lated dementia, Huntington's disease, normal pressure hydrocephalus, HIV infection, syphilis, subdural haematoma, and some cerebral tumours.

AETIOLOGY/ RISK FACTORS

Alzheimer's disease: The cause of Alzheimer's disease is unclear. A key pathological process is deposition of abnormal amyloid in the central nervous system. [10] Another early change is abnormal phosphorylation of tau; an intracellular structural protein. This results in apoptosis and neurofibrillary tangles. Disease-modifying agents in development target both processes. Most people with the relatively rare condition of early-onset Alzheimer's disease (before age 60 years) exhibit an autosomal-dominant inheritance owing to mutations in presenilin or amyloid precursor protein genes. Several gene mutations (on APP, PS-1, and PS-2 genes) have been identified. Later-onset dementia is sometimes clustered in families, but specific gene mutations have not been identified. Down's syndrome, cardiovascular risks, and lower premorbid intellect may be risk factors for Alzheimer's disease. Alzheimer's disease and vascular pathology frequently co-exist. **Vascular dementia:** Vascular dementia is related to cardiovascular risk factors, such as smoking, arteriosclerosis, hypertension, and diabetes. **Lewy body dementia:** Lewy body dementia is characterised by the presence of Lewy bodies (abnormal intracellular inclusions consisting of alpha-synuclein) in the cortex. Brain acetylcholine activity is reduced in many forms of dementia, and the level of reduction correlates with cognitive impairment. [1] [6]

PROGNOSIS

Alzheimer's disease: Alzheimer's disease usually has an insidious onset with progressive reduction in cerebral function. Diagnosis is difficult in the early stages. Median life expectancy after diagnosis is about 6 years, although many people live far longer. [11] **Vascular dementia:** We found no reliable data on prognosis. **Lewy body dementia:** People with Lewy body dementia have an average life expectancy of about 6 years after diagnosis. [5] Behavioural problems, depression, and psychotic symptoms are common in all types of dementia. [12] [13] Eventually, most people with dementia find it difficult to perform simple tasks without help.

AIMS OF INTERVENTION

To improve cognitive function (memory, orientation, attention, and concentration); to reduce behavioural and psychological symptoms (wandering, aggression, anxiety, depression, and psychosis); to improve quality of life for both the individual and carer, with minimum adverse effects.

OUTCOMES

Primary outcomes are quality of life, time to institutionalisation or death, scales of cognitive function, global assessment of function, functional scores, and behavioural and psychological symptoms. **Cognitive symptoms and global assessment of function:** Comprehensive scales of cognitive function (e.g., Alzheimer's Disease Assessment Scale cognitive subscale [ADAS-cog]: 70-point scale, lower scores indicate better function; [14] Mini Mental State Examination [MMSE]: 30-point scale, lower scores indicate worse function; [15] Clinical Dementia Rating Scale [CDR], 5-point scale assessing six cognitive and functional parameters, higher scores indicate worse function; [16] Alzheimer's Disease Functional Assessment and Change Scale [ADFACS]: 7-point scale, higher scores indicate worse function; [16] and Severe Impairment Battery: 100-point scale used in people with severe Alzheimer's disease, lower scores indicate worse function). [17] It has been suggested that ADAS-cog may be more sensitive than MMSE in assessing dementia, but neither scale directly reflects outcomes important to people with dementia or their carers. Most clinical trials in mild to moderate dementia use the ADAS-cog as the primary outcome for cognition. The ADAS-cog is a 70-point scale; a 2- or 3-point change on this scale is likely to represent only a marginal clinical significance, although the large studies undertaken in dementia have sufficient power to find highly statistically significant differences in what amounts to minimal clinical change. Measures of global state include Clinical Global Impression of Change (CGI-C) with carer input scale and Clinician's Interview Based Impression of Change-Plus (CIBIC-Plus), which provides a rating using a 7-point scale. Gottfries–Brane–Steen (GBS) is a global assessment tool for evaluating dementia symptoms (score ranges from 0 to 156; higher scores indicate worse function). **Functional scores:** These include the Disability Assessment for Dementia (DAD), a 40-item scale assessing 10 domains of function, [18] and the Instrumental Activities of Daily Living Scale, maximum score 14 (lower scores indicate worse function). [19] **Behavioural and psychological symptoms:** Measures of psychiatric symptoms (e.g., Neuropsychiatric Inventory [NPI]: 120-point scale, higher scores indicate greater difficulties; 12-item carer-rated scale: maximum score 144, higher scores indicate greater difficulties; Dementia Mood Assessment Scale and Brief Psychiatric Rating Scale: higher scores indicate greater difficulties; Behavioral Pathology in Alzheimer's Disease Rating (BEHAVE-AD) scale: scores 0–75, higher scores indicate greater difficulties; Behavioural Rating Scale for Geriatric Patients: scale rating 35 aspects of behaviour, score from 0 to 2, higher score indicates worse function). **Quality of life** of the person with dementia or their carer (rarely used in clinical trials). Quality of life and **time to institutionalisation or death** are rarely reported because of the short duration of most trials. [16]

METHODS *Clinical Evidence* search and appraisal April 2008. The following databases were used to identify studies for this systematic review: Medline 1988 to April 2008, Embase 1988 to April 2008, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials, Issue 1, 2008. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), and NICE. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single blinded, and containing more than 50 individuals of whom more than 80% were followed up. The minimum length of follow-up required to include studies was at least 6 weeks for non-drug trials and at least 12 weeks for drug trials. We excluded all studies described as "open", "open label", or not blinded, unless blinding was impossible (e.g., non-drug psychotherapy). We also did a cohort harms search for specific harms of atypical antipsychotics. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. **Symptom reporting:** Dementia is often considered to have two domains of symptoms: cognitive impairment and non-cognitive symptoms (behavioural and psychological symptoms). We have separated the evidence into these two domains because they are often therapeutic targets at different stages of dementia, and many RCTs focus on one or other domain of symptoms. **Quality issues relating to included RCTs:** In many RCTs, missing data were managed using "last observation carried forwards", which does not account for the tendency of people with dementia to deteriorate with time. These RCTs may overestimate the benefit derived from interventions, especially when there are higher withdrawal rates in the intervention arm compared with controls. We found few RCTs in people with types of dementia other than Alzheimer's disease. The authors assessed studies on an individual basis to identify studies that were of sufficient methodological rigour and not subject to obvious bias. Not all systematic reviews identified were reported in each option. For each option, the authors selected the most recent and methodologically sound review and reported this in detail. Older reviews that were superseded by later reviews, or did not add any further important data above that already presented in included reviews, were not reported. Where a systematic review was included in an option, subsequent RCTs were reported sparingly. **Limitations to generalisability of included RCTs:** Participants in RCTs of treatments for dementia are often not representative of all people with dementia. Few RCTs are conducted in primary care and few are conducted in people with types of dementia other than Alzheimer's disease. Most RCTs are 6 months or less in duration, compared with a disease duration of many years, and most are conducted in mild to moderate dementia. Attrition and methodological difficulties often preclude longer trials in this patient group. This review reports placebo-controlled comparisons. The next version of the review will also include comparisons between active treatments. **General reporting:** To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 22). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com). **Changes at this update:** Since the last published version of this review, the review has been completely restructured and coverage broadened, a backsearch to 1988 has been undertaken and previously reported evidence has been re-evaluated, new evidence up to the current search date of April 2008 has been added, and the minimum size criteria for inclusion of individual studies in this review has been raised (from 20 to 50 people).

QUESTION **What are the effects of treatments on cognitive symptoms of dementia (Alzheimer's, Lewy body, or vascular)?**

OPTION **ACETYLCHOLINESTERASE INHIBITORS (DONEPEZIL, GALANTAMINE, RIVASTIGMINE) VERSUS PLACEBO IN PEOPLE WITH COGNITIVE SYMPTOMS OF DEMENTIA** New

Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)
Compared with placebo in people with Alzheimer's disease Acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) may be more effective than placebo at improving cognitive function scores, global function scores, and activities of daily living scores in people with Alzheimer's disease (low-quality evidence).

Compared with placebo in people with vascular dementia Acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) may be marginally more effective than placebo at improving cognitive function scores at 6 months in people with vascular dementia, but not global function scores or activities of daily living scores (low-quality evidence).

Compared with placebo in people with Lewy body dementia We don't know whether rivastigmine is more effective than placebo at improving cognitive-function scores, global function scores, or activities of daily living scores in people with Lewy body dementia (very low-quality evidence).

Note
Acetylcholinesterase inhibitors may be associated with adverse effects, including GI adverse effects (e.g., nausea, vomiting, diarrhoea, anorexia).

For GRADE evaluation of interventions for dementia, see table, p 22 .

Benefits:

Acetylcholinesterase inhibitors versus placebo in people with Alzheimer's disease:
We found two systematic reviews comparing acetylcholinesterase inhibitors as a group versus placebo and pooled data [20] [21] and one subsequent RCT. [22]

The first review (search date 2005; 13 multicentre double-blind RCTs; people with mild, moderate, or severe Alzheimer's disease) included RCTs in which treatment had been given for 6 months or longer, and at the dose recommended as optimal by the manufacturing pharmaceutical company. [20] It performed an intention-to-treat analysis, and where full data were not available, it performed an analysis with the last observation carried forwards. The review found that people leaving before the end of studies ranged from 16% to 43% in the treatment group and 0% to 30% in the placebo group. The review found that acetylcholinesterase inhibitors significantly improved cognitive outcomes compared with placebo at 6 months or later (Alzheimer's Disease Assessment Scale cognitive subscale [ADAS-cog]: 10 RCTs, 4236 people; WMD –2.4, 95% CI –2.0 to –2.7; Mini Mental State Examination [MMSE]: 9 RCTs, 3118 people; WMD 1.4, 95% CI 1.1 to 1.6). [20] There was significant heterogeneity among RCTs included in both analysis. The review reported that in one analysis (MMSE), this resulted from one RCT (466 people) that found a larger treatment effect than other RCTs. It also found that acetylcholinesterase inhibitors significantly improved global assessment compared with placebo at 6 months (Clinician's Interview Based Impression of Change-Plus [CIBIC-Plus] scale; number of people improved: 8 RCTs, 428/1755 [24%] with acetylcholinesterase inhibitor *v* 277/1647 [17%] with placebo; OR 1.6, 95% CI 1.3 to 1.9). The review found that acetylcholinesterase inhibitors significantly improved activities of daily living scores compared with placebo at 6 months or later (Progressive Deterioration Scale [scale 0–100]: 5 RCTs [donepezil, rivastigmine], 2188 people; WMD 2.4, 95% CI 1.6 to 3.3; Disability Assessment for Dementia [DAD] scale: 2 RCTs [donepezil, galantamine], 663 people; WMD 4.4, 95% CI 0.8 to 1.9). The review did not provide a subgroup analysis by individual agent versus placebo (see comment below). [20]

The second review (search date 2002) performed a slightly different analysis. It included double-blind RCTs using any dose of acetylcholinesterase inhibitor where treatment had been given for at least 12 weeks. [21] It found that acetylcholinesterase inhibitors significantly increased cognitive responders compared with placebo (defined as an improvement of 4 points or more on ADAS-cog: 5 RCTs, 2419 people; mean difference in proportions 10%, 95% CI 4% to 17%; NNT 10, 95% CI 8 to 15). There was significant heterogeneity among RCTs in the analysis due to one included RCT which was unexplained. [21] The review found that acetylcholinesterase inhibitors significantly increased global responders compared with placebo (defined as improved on global scale such as CIBIC-Plus or Clinical Global Impression of Change [CGI-C]: 8 RCTs, 4205 people; mean difference in proportions 9%, 95% CI 6% to 12%; NNT 12, 95% CI 9 to 16). One RCT was excluded from this analysis owing to heterogeneity; it was undertaken exclusively in Japanese people and showed a large treatment effect. [21] The subsequent RCT (343 people with severe Alzheimer's disease) found that donepezil significantly improved cognitive and global outcomes compared with placebo at 24 weeks (Severe Improvement Battery score; percentage with improvement or no change: 63% with donepezil *v* 39% with placebo; absolute numbers not reported; results presented graphically; P = 0.001; CIBC-Plus [improved, no change, worsened]; results presented graphically; P = 0.047). [22] It found no significant difference between groups in activities of daily living scores (Alzheimer's Disease Cooperative Study-Activities of Daily Living scale for severe AD [ADCS-ADL-sev]; P = 0.36). [22]

Acetylcholinesterase inhibitors versus placebo in people with vascular dementia:
We found one systematic review (search date 2006; 6 RCTs; vascular dementia of mild–moderate severity; 24–28 weeks' duration), which included both published and unpublished RCTs and pooled data by individual agents, rather than by acetylcholinesterase inhibitors as a group. [23] One RCT of galantamine also included people with Alzheimer's and vascular disease, from which subgroup data for those people with vascular dementia was extracted. All RCTs were double blinded, but

reporting of allocation concealment and randomisation method varied among RCTs, and some were of poor quality. It found that donepezil, galantamine, and rivastigmine all significantly improved cognition scores compared with placebo (ADAS-cog: donepezil 10 mg: 2 RCTs, 763 people; WMD –2.2, 95% CI –3.0 to –1.4; galantamine 24 mg: 2 RCTs, 966 people; WMD –1.6, 95% CI –2.4 to –0.8; rivastigmine 12 mg: 1 RCT, 368 people; WMD –1.10, 95% CI –2.15 to –0.05). [23] However, it found no significant difference between groups in global outcomes (CIBIC-Plus or CGI-C [improvement or no change]: donepezil 10 mg: 2 RCTs, 785 people; OR 1.2, 95% CI 0.9 to 1.6; galantamine 24 mg: 2 RCTs, 943 people; OR 1.1, 95% CI 0.8 to 1.42; rivastigmine 12 mg: 1 RCT, 649 people; OR 1.0, 95% CI 0.8 to 1.4). It found that donepezil 10 mg significantly improved activities of daily living scores compared with placebo, but not donepezil 5 mg (Alzheimer's Disease Functional Assessment and Change Scale [ADFACS]: donepezil 10 mg; –0.95, 95% CI –0.16 to –1.74; donepezil 5 mg; –0.73, 95% CI –1.53 to +0.07; no further details reported). It also found no significant difference between groups in activities of daily living scores for galantamine or rivastigmine (ADCS-ADL/DAD: galantamine: –0.04, 95% CI –0.27 to + 0.20; ADCS-ADL: rivastigmine: –0.05, 95% CI –0.20 to +0.09; no further details reported). [23] The review concluded that the acetylcholinesterase inhibitors produced small benefits in cognition of uncertain clinical significance and that more specific patient level information was needed on treatment responses across different types and severities of vascular dementia.

Acetylcholinesterase inhibitors versus placebo in people with Lewy body dementia:
We found one systematic review (search date 2006), which found one RCT (120 people) comparing rivastigmine versus placebo for 20 weeks. [24] The review found that rivastigmine significantly improved activities of daily living scores compared with placebo (activities of daily living, power of attention, 83 people in analysis, SMD –0.52, 95% CI –0.08 to –0.96), but found no significant difference between groups in cognitive outcomes or global functioning (MMSE: difference in change score favouring drug; absolute numbers not reported; P = 0.72; CGC-Plus: good, moderate, or minimal improvement: P = 0.085; absolute numbers not reported). However, the activities of daily living analysis was based on 83/120 (69%) people, which is below the minimum follow-up of 80% for this review. [24]

Harms:

Acetylcholinesterase inhibitors versus placebo in people with Alzheimer's disease:
The review found that acetylcholinesterase inhibitors significantly increased the proportion of people who withdrew before the end of treatment (withdrawal before the end of treatment: 13 RCTs; 778/2672 [29%] with acetylcholinesterase inhibitors *v* 453/2471 [18%] with placebo; OR 1.8, 95% CI 1.5 to 2.0; withdrawal before the end of treatment due to adverse effect: 13 RCTs; 488/2672 [18%] with acetylcholinesterase inhibitors *v* 209/2471 [8%] with placebo; OR 2.3, 95% CI 2.0 to 2.8). [20] It found that during treatment for 6 months or more, compared with placebo, acetylcholinesterase inhibitors significantly increased the proportion of people with at least one adverse effect of: abdominal pain, anorexia, diarrhoea, dizziness, fatigue, headache, insomnia, nausea, tremor, vomiting, or weight loss (abdominal pain: 7 RCTs, 2703 people; OR 2.0, 95% CI 1.5 to 2.6; anorexia: 10 RCTs, 4419 people; OR 3.8, 95% CI 2.9 to 4.9; diarrhoea: 13 RCTs, 5173 people; OR 1.9, 95% CI 1.6 to 2.3; dizziness: 12 RCTs, 4583 people; OR 2.0, 95% CI 1.6 to 2.4; fatigue: 1 RCT, 319 people; OR 4.4, 95% CI 1.2 to 15.9; headache: 9 RCTs, 3686 people; OR 1.6, 95% CI 1.3 to 1.9; insomnia: 7 RCTs, 2905 people; OR 1.5, 95% CI 1.1 to 2.0; nausea: 13 RCTs, 5089 people; OR 4.9, 95% CI 4.1 to 5.7; tremor: 2 RCTs, 633 people; OR 6.8, 95% CI 2.0 to 23.4; vomiting: 11 RCTs, 4703 people; OR 4.8, 95% CI 3.9 to 5.9; weight loss: 4 RCTs, 1358 people; OR 3.0, 95% CI 1.9 to 4.8). It found no significant difference between groups in abnormal gait, accidental injury, agitation, anxiety, arthralgia, back pain, confusion, conjunctivitis, constipation, cough, depression, ecchymosis, fever, fracture, hostility, infection, pain, rash, skin ulcer, respiratory tract infection, or UTI. [20]

The second review found that acetylcholinesterase inhibitors significantly increased adverse effects (14 RCTs, 6784 people; NNH 12, 95% CI 10 to 18), and people who 'dropped out' due to adverse effects (7952 people; NNH 16, 95% CI 13 to 19). [21] Both analyses were heterogeneous, which was reported to be possibly due to different titration schedules, protocol differences, or random variation between included RCTs. [21] The subsequent RCT reported that approximately three-quarters of people experienced a severe event (80% with donepezil *v* 70% with placebo) and most adverse effects (70%) were rated as mild or moderate (statistical analysis between groups not reported). [22] The most common adverse effects were diarrhoea, anorexia, nausea, agitation, and vomiting (diarrhoea: 10% with donepezil *v* 4% with placebo; anorexia: 7% with donepezil *v* 4% with placebo; nausea: 7% with donepezil *v* 2% with placebo; agitation: 6% with donepezil *v* 6% with placebo; vomiting: 6% with donepezil *v* 2% with placebo; statistical analysis between groups not reported). [22]

Acetylcholinesterase inhibitors versus placebo in people with vascular dementia:
The review found that rates of discontinuation for adverse effects were significantly higher in the acetylcholinesterase inhibitor groups compared with placebo (donepezil 10 mg: OR 2.1, 95% CI

1.4 to 3.2; galantamine: OR 2.4, 95%, CI 1.7 to 3.5; rivastigmine: OR 2.7, 95% CI 1.5 to 4.6). [23] It reported that in one RCT, the risk of death was significantly higher with donepezil (11/678 [1.7%] with donepezil *v* 0/326 [0%] with placebo; OR 4.6, 95% CI 1.3 to 16.1). After pooling data from all three RCTs of donepezil, the review found no significant difference between groups in death (OR 1.4, 95% CI 0.7 to 3.0). The RCTs were heterogeneous for this outcome, possibly due to a high death rate (3.5%) in the placebo arm of one RCT. [23] The review found that adverse effects were inconsistently reported and numbers were low, although the acetylcholinesterase inhibitors were broadly associated with a significantly increased risk of GI events (such as nausea, vomiting, diarrhoea, and anorexia). [23]

Acetylcholinesterase inhibitors versus placebo in people with Lewy body dementia:
The review found that rivastigmine significantly increased the risk of any adverse event compared with placebo (120 people; NNH 7, 95% CI 4 to 34). [24]

Comment:

The meta-analyses were quite restrictive in study selection; the authors of the systematic reviews raise concerns about the quality and reporting of many trials. The overall effect size of less than 3 points on the ADAS-cog is barely clinically significant, although this represents an average, and some people derive significant clinical benefit. More studies are needed on individuals with vascular and Lewy body dementia.

We found three further systematic reviews on the effects of donepezil, [25] rivastigmine, [26] and galantamine [27] alone in people with Alzheimer's disease. The reviews found similar significant improvements with each acetylcholinesterase inhibitor alone versus placebo in cognition scores at 24 to 26 weeks (ADAS-cog: donepezil 5 mg: 3 RCTs, 906 people; WMD –2.0, 95% CI –2.8 to –1.3; donepezil 10 mg: 5 RCTs, 848 people; WMD –2.8, 95% CI –3.5 to –2.1; [25] galantamine 24 mg: 4 RCTs, 1630 people; WMD –3.1, 95% CI –3.7 to –2.6; [27] rivastigmine 6–12 mg: 4 RCTs, 1917 people; WMD –2.1, 95% CI –2.7 to –1.5). [26]

OPTION GINKGO BILOBA VERSUS PLACEBO IN PEOPLE WITH COGNITIVE SYMPTOMS OF DEMENTIA

New

Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)
Compared with placebo Ginkgo biloba may be no more effective than placebo at improving cognitive function scores at 22 to 26 weeks in people with Alzheimer's disease and multiple infarct dementia. We don't know whether ginkgo biloba is more effective than placebo at improving global function scores or activities of daily living scores at 22 to 28 weeks in people with dementia or cognitive impairment, as results were inconsistent and varied by the exact analysis performed (very low-quality evidence).

For GRADE evaluation of interventions for dementia, see table, p 22 .

Benefits:

Ginkgo biloba versus placebo:
We found one systematic review (search date 2006), which included RCTs in any type of dementia or mild cognitive impairment. [28] It did not separately analyse data by type of dementia, but pooled results for all RCTs. It noted that some included RCTs included people with any type of dementia or cognitive impairment, although others were more selective and applied appropriate diagnostic criteria. The review performed multiple analyses by dose, length of treatment, and outcome measure. We have selectively reported outcomes at longer term (22–28 weeks) assessed by our outcome measures of choice. The review found no significant difference between ginkgo and placebo in cognitive outcomes measured by Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) score at 22 to 26 weeks (ginkgo at any dose: 2 RCTs [mainly Alzheimer's disease, also multiple infarct dementia], 783 people; WMD –0.18, 95% CI –0.98 to +0.62). [28] However, there was significant heterogeneity in this result, with both RCTs showing treatment effects in different directions. The review found that ginkgo significantly increased global improvement compared with placebo at 24 to 28 weeks, but only at doses above 200 mg daily (Clinical Global Impression of Change [CGI-C]-improved or unchanged compared with baseline: doses less than 200 mg/day: 2 RCTs [mainly Alzheimer's disease, also multiple infarct dementia], 652 people; OR 1.3, 95% CI 0.9 to 1.7; doses greater than 200 mg/day: 2 RCTs [mainly Alzheimer's disease, also multiple infarct dementia], 549 people, OR 1.7, 95% CI 1.1 to 2.5). The review found that ginkgo at any dose significantly improved activities of daily living scores compared with placebo at 22 to 24 weeks, but found no significant difference between high-dose ginkgo (greater than 200 mg/day) and placebo (variety of measures: any dose: 4 RCTs [mainly Alzheimer's disease, also multiple infarct dementia, other dementias, and cognitive impairment], 1111 people; SMD –0.14, 95% CI –0.02 to –0.26; greater than 200 mg/day: 3 RCTs [mainly Alzheimer's disease, also multiple infarct dementia, other dementias, and cognitive impairment], 632 people; SMD –0.06, 95% CI –0.22 to +0.09). However, these data excluded one RCT which introduced heterogeneity because of an extreme result, and some measures reported by RCTs ostensibly as "activities of daily living" assessed additional areas such as cognition, social, and mood items. [28]

Harms:

Ginkgo biloba versus placebo:
The review found no significant difference between ginkgo and placebo in adverse effects at 12 or 24 weeks (12 weeks: 11 RCTs, 1062 people; OR 0.9, 95% CI 0.6 to 1.4; 24 weeks: dose less than 200 mg/day: 4 RCTs, 793 people; OR 0.9, 95% CI 0.6 to 1.2; dose greater than 200 mg/day: 2 RCTs, 744 people; OR 0.71, 95% CI 0.49 to 1.01). [28]

Comment:

Many earlier studies were of poor methodological quality, and there was significant clinical and statistical heterogeneity between RCTs. [28] With regard to all included studies and analyses, the review noted that several earlier smaller studies that found positive effects with ginkgo had not been confirmed in more recent trials, it was unable to exclude the possibility of publication bias, and that the evidence that ginkgo has predictable and clinically significant benefit for people with dementia or cognitive impairment was inconsistent and unconvincing. [28]

OPTION MEMANTINE VERSUS PLACEBO IN PEOPLE WITH COGNITIVE SYMPTOMS OF DEMENTIA

N e w

Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)
Compared with placebo Memantine may be marginally more effective than placebo at improving cognitive function scores and global function scores at 24 to 28 weeks in people with moderate to severe or mild to moderate Alzheimer's disease. Memantine may be marginally more effective than placebo at improving activities of daily living scores in people with moderate to severe Alzheimer's disease, but not in people with mild to moderate Alzheimer's disease. Memantine may be marginally more effective at improving cognitive function scores at 28 weeks in people with vascular dementia, but not global function scores or activities in daily living scores. However, although studies found a statistical improvement in scores with memantine for some of these outcomes, the clinical importance of these improvements are unclear (very low-quality evidence).

For GRADE evaluation of interventions for dementia, see table, p 22 .

Benefits:

Memantine versus placebo:
We found three systematic reviews, which pooled data, but employed different inclusion criteria and performed different analyses. [29] [30] [31] We therefore report all three reviews here.

The first review (search date 2006) included double-blind RCTs of any length, dosage, and included unpublished data. [29] In people with moderate to severe Alzheimer's disease, it found that memantine 20 mg daily significantly improved cognitive and global outcomes compared with placebo at 24 to 28 weeks, although the effects were small (Severe Impairment Battery [100-point scale]: 3 RCTs, 976 people; WMD 3.0, 95% CI 1.7 to 4.3; CIBC-Plus: 3 RCTs, 964 people; WMD 0.3, 95% CI 0.2 to 0.4). [29] The RCTs in the cognitive result were heterogeneous, which was due to widely differing results in two RCTs. [29] The review found that memantine significantly improved activities of daily living scores at 24 to 28 weeks (Alzheimer's Disease Cooperative Study-Activities of Daily Living scale for severe AD [ADCS-ADL-sev19] [54-point scale]: 3 RCTs, 978 people; WMD 1.3, 95% CI 0.4 to 2.1). In people with mild to moderate Alzheimer's disease, the review found a significant improvement with memantine 20 mg daily in cognition scores and global outcomes at 24 weeks compared with placebo (Alzheimer's Disease Assessment Scale cognitive subscale [ADAS-cog]: 3 RCTs, 1379 people; WMD 0.99, 95% CI 0.21 to 1.78; CIBC-Plus: 3 RCTs, 1381 people; WMD 0.13, 95% CI 0.01 to 0.25). It found no significant difference between groups in activities of daily living scores (ADCS-ADL23: 3 RCTs, 1371 people; WMD +0.2, 95% CI –0.9 to +1.27). In people with vascular dementia, the review found that memantine (20 mg/day) produced a small but significant improvement in cognition at 28 weeks (ADAS-cog: 2 RCTs, 815 people; WMD 1.8, 95% CI 0.9 to 2.8), but found no significant difference between groups in global outcomes or activities of daily living (Clinical Global Impression [CGI]: 2 RCTs, 775 people; WMD +0.03, 95% CI –0.13 to +0.19; Nurses' Observation Scale for Geriatric Patients [NOSGER] self-care subscale: 2 RCTs, 542 people; WMD +0.12, 95% CI –0.43 to +0.67). All analyses were based on intention to treat with the last observation carried forwards. [29]

The second review (search date 2004) included double-blind RCTs of at least 6 months' duration in Alzheimer's disease only. [30] It included two published RCTs, one RCT presented as a poster, and three unpublished RCTs. Five RCTs used memantine 20 mg daily and one RCT used 40 mg daily. Overall, in people with mild to severe Alzheimer's disease, it found that memantine significantly improved cognition scores, global scores, and activities of daily living scores (cognition: 6 RCTs, 2255 people; SMD –0.21, 95% CI –0.08 to –0.34; global status: 6 RCTs, 2245 people; SMD –0.19, 95% CI –0.10 to –0.27; activities of daily living: 6 RCTs, 2249 people; SMD –0.10, 95% CI –0.01 to –0.18). [30] The analysis for cognition score was heterogeneous, which was due to the most positive outlier RCT (247 people). [30] All analyses were based on intention to treat, with the last observation carried forwards. Of the six included RCTs, only two were published, one being presented as a poster, and the remaining three RCTs were from information on file.

The third review (search date 2005) only included published RCTs of any duration in people with Alzheimer's disease or vascular dementia. [31] It included six phase III RCTs and excluded three phase II RCTs, as it reported that it was trying to assess the clinical meaningfulness of the drug, and as phase II RCTs were addressing primarily safety and pharmacokinetic issues, that these RCTs were not directly applicable. It found that memantine significantly improved outcomes compared with placebo (5 RCTs of at least 6 months' duration: cognition: SMD –0.33, 95% CI –0.42 to –0.23; global impression: SMD –0.74, 95% CI –0.86 to –0.61; function: SMD –0.11, 95% CI –0.21 to –0.01; absolute numbers not reported for any analysis; see comment below). [31]

Harms:

Memantine versus placebo:
The first review reported adverse effects by different population groups rather than overall figures. [29] It reported that memantine was "well tolerated", and found no significant difference between memantine and placebo in people suffering at least one adverse effect, or between groups in falls or depression. [29] One RCT found memantine significantly increased somnolence (14/201 [7%] with memantine *v* 2/202 [1%] with placebo; OR 7.5, 95% CI 1.7 to 33.3). [29]

The second review found no significant difference between memantine and placebo in treatment discontinuation caused by adverse effects (P = 0.86), in people having any adverse effect (P = 0.42), or in people having a serious adverse effect (P = 0.89). [30] It found that, compared with placebo, memantine significantly increased constipation, somnolence, vomiting, hypertension, and abnormal gait (constipation: 3.6% with memantine *v* 2.5% with placebo; OR 1.62, 95% CI 1.01 to 2.60; somnolence: 3.8% with memantine *v* 2.3% with placebo; OR 1.81, 95% CI 1.13 to 2.90; vomiting: 3.3% with memantine *v* 2.1% with placebo; OR 1.77, 95% CI 1.07 to 2.94; hypertension: 4.3% with memantine *v* 2.9% with placebo; OR 1.60, 95% CI 1.03 to 2.47; abnormal gait: 3.2% with memantine *v* 2.1% with placebo; OR 1.70, 95% CI 1.02 to 2.83). [30]

The third review did not report on adverse effects. [31]

Comment:

Memantine appears well tolerated. Although reviews report statistically significant results, the effect size is small, and at best confers only minimal clinically meaningful benefit on the treatment of cognitive symptoms of dementia.

OPTION NON-PHARMACOLOGICAL INTERVENTIONS (COGNITIVE STIMULATION, MUSIC THERAPY, REMINISCENCE THERAPY) VERSUS PLACEBO IN PEOPLE WITH COGNITIVE SYMPTOMS OF DEMENTIA New

Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)
Reminiscence therapy compared with placebo or no treatment Reminiscence therapy may be more effective than placebo at improving cognition function scores at 4 to 6 weeks in people with dementia (type and severity unspecified), but we don't know about longer term. However, RCTs had important methodological weaknesses, which limits any conclusions that can be drawn (very low-quality evidence).

Note
We found no direct information from RCTs about music therapy or cognitive stimulation in the treatment of people with cognitive symptoms of dementia (Alzheimer's, Lewy body, or vascular).

For GRADE evaluation of interventions for dementia, see table, p 22 .

Benefits:

Reminiscence therapy versus placebo or no treatment:
We found one systematic review of reminiscence therapy (search date 2004; 4 RCTs; 144 people with evaluable data; therapy for 4–18 weeks for 1–5 times/week). [32] The RCTs in the meta-analysis provided incomplete data on the type or severity of dementia. [32] The review found that reminiscence therapy improved cognition compared with no reminiscence therapy at 4 to 6 weeks (4 RCTs, 93 people; SMD 0.50, 95% CI 0.07 to 0.92). The review noted that each RCT included a different type of reminiscence therapy, and that included RCTs had important methodological weaknesses. [32] None of the individual RCTs met our inclusion criteria for this review. The primary studies lacked adequate controls, had potential for bias, used diverse interventions, and used inadequate outcome measures.

Music therapy versus placebo or no treatment:
We found one systematic review (search date 2006) of music therapy, which found no RCTs of sufficient quality. [33]

Cognitive stimulation versus placebo/no treatment:
We found one systematic review (search date 2006), which found no RCTs of sufficient quality in our population of interest. [24]

Harms:

Reminiscence therapy versus placebo or no treatment:
The review did not report on harms. [32]

Music therapy versus placebo or no treatment:
We found no RCTs.

Cognitive stimulation versus placebo or no treatment:
We found no RCTs.

Comment: None.

OPTION OMEGA 3 (FISH OIL) VERSUS PLACEBO IN PEOPLE WITH COGNITIVE SYMPTOMS OF DEMENTIA New

Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)
Compared with placebo Omega 3 fish oil (docosahexanoic acid plus eicosapentaenoic acid) may be no more effective than placebo at improving cognitive or global function scores at 6 months in people with mild to moderate Alzheimer's disease (low-quality evidence).

For GRADE evaluation of interventions for dementia, see table, p 22 .

Benefits:

Omega 3 (fish oil) versus placebo:
We found one RCT (174 people with mild to moderate Alzheimer's disease) comparing docosahexanoic acid (DHA) plus eicosapentaenoic acid (EPA) versus placebo. [34] It found no significant difference between groups in cognitive or global outcomes at 6 months (Mini Mental State Examination [MMSE] mean score [0–30 points]: 22.8 with active intervention *v* 22.4 with placebo; Alzheimer's Disease Assessment Scale cognitive subscale [ADAS-cog] mean score [0–85 points]: 27.7 with active intervention *v* 28.3 with placebo; Clinical Dementia Rating [CDR] scale, mean global score [0–3 points]): 1.1 with active intervention *v* 1.1 with placebo; all reported as not significant; P values not reported). [34]

Harms:

Omega 3 fish oil versus placebo:
The RCT reported that the fatty acid preparation was "well tolerated and safe". [34] Reasons for leaving the RCT were diarrhoea (9 people), dysphagia (9 people), new serious somatic disease (10 people), non-compliance (1 person), and one person withdrew informed consent (numbers in individual groups and statistical analysis between groups not reported). [34]

Comment: Although we found a few studies looking at prevention of dementia using omega 3 fish oil, there is a need for more studies on treatment of established dementia.

OPTION STATINS VERSUS PLACEBO IN PEOPLE WITH COGNITIVE SYMPTOMS OF DEMENTIA New

Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)
Compared with placebo Atorvastatin may be more effective than placebo at improving cognitive function scores at 6 months in people with mild to moderate Alzheimer's disease, but not at 12 months. Atorvastatin may be no more effective than placebo at improving global function scores at 6 and 12 months or activities of daily living scores at 12 months in people with mild to moderate Alzheimer's disease (low-quality evidence).

For GRADE evaluation of interventions for dementia, see table, p 22 .

Benefits:

Statins versus placebo:
We found one RCT comparing atorvastatin versus placebo in 71 people with mild to moderate Alzheimer's disease. [35] The RCT found that atorvastatin significantly improved cognitive outcomes at 6 months, but not at 12 months (mean Alzheimer's Disease Assessment Scale cognitive subscale [ADAS-cog]: 6 months, about 3.5 points difference between groups; P = 0.003; 12 months, about 3.5 points difference between groups; P = 0.055; absolute numbers not reported, results presented graphically). It found no significant difference between groups in global improvement at 6 and 12 months (Clinical Global Impression of Change [CGI-C]: 6 months; P = 0.62; 12 months; P = 0.07; absolute numbers not reported, results presented graphically). It found no significant difference between groups in activities of daily living at 12 months (ADCL-ADL: P = 0.23; absolute numbers not reported). [35]

Harms:

Statins versus placebo:
The RCT did not report on harms. [35]

Comment: Statins may be useful in prevention of dementia as they modify known risk factors for dementia. However, more evidence is needed, and prevention trials are difficult.

OPTION NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) VERSUS PLACEBO IN PEOPLE WITH COGNITIVE SYMPTOMS OF DEMENTIA New

Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)
Compared with placebo Naproxen and celecoxib seem no more effective than placebo at improving cognitive function scores or global function scores at 1 year in people with mild to moderate Alzheimer's disease, and naproxen seems no more effective than placebo at improving activities of daily living scores at 1 year (moderate-quality evidence).

Note
We found no direct evidence from RCTs on NSAIDs other than naproxen and celecoxib.

For GRADE evaluation of interventions for dementia, **see table, p 22 .**

Benefits:

NSAIDs versus placebo:
We found three systematic reviews on aspirin (search date 2005) in people with vascular dementia, [36] ibuprofen (search date 2002) in Alzheimer's disease, [37] and indometacin (indomethacin; search date 2004) [38] in Alzheimer's disease, which found no RCTs of sufficient quality. We found one RCT on naproxen [39] and one RCT on celecoxib. [40] The first RCT (351 people; mild to moderate Alzheimer's disease) compared three treatments: rofecoxib (122 people), naproxen (118 people), and placebo (111 people). [39] We have not reported any results on rofecoxib as the drug has been withdrawn. The RCT found no significant difference between naproxen and placebo in cognitive scores, global symptom scores, activities of daily living, or quality of life at 1 year (cognitive scores measured by Alzheimer's Disease Assessment Scale cognitive subscale [ADAS-cog]: P = 0.96; global symptom scores measured by CDR-SOB: P = 0.89; activities of daily living measured by Alzheimer's Disease Cooperative Study-Activities of Daily Living [ADCS-ADL] scale: P = 0.14; quality of life measured by Quality of Life–Alzheimer's Disease [QOL-AD]; P = 0.93). [39] The second RCT (425 people with mild to moderate Alzheimer's disease) compared celecoxib twice daily versus placebo over 52 weeks. [40] The RCT found no significant differences between groups in cognitive outcomes or global outcomes at 1 year (ADAS-cog; P = 0.54; Clinician's Interview Based Impression of Change-Plus [CIBIC-Plus] scores; P = 0.45). [40]

Harms:

NSAIDs versus placebo:
The first RCT found that naproxen significantly increased the proportion of people with hypertension compared with placebo (5% with naproxen *v* 0% with placebo; P =0.03). [39] It found that more people had fatigue, dizziness, and dry mouth with naproxen than with placebo, although differences between groups were not significant (P = 0.06 for all comparisons). [39] The second RCT found that, compared with placebo, celecoxib significantly increased dyspnoea, dyspepsia, and urinary incontinence (dyspnoea: 3.9% with celecoxib *v* 0% with placebo; dyspepsia: 3.2% with celecoxib *v* 0% with placebo; urinary incontinence: 3.2% with celecoxib *v* 0% with placebo; all comparisons; P less than 0.05), although more people had hernia with placebo than celecoxib (2.1% with celecoxib *v* 0% with placebo; P less than 0.05). [40] In total, 73 (25.6%) people with celecoxib and 32 (22.9%) with placebo experienced serious adverse effects (statistical analysis between groups not reported). The RCT reported the most frequently reported serious adverse effects reported were confusion, UTI, accidental fracture, pneumonia, cardiac failure, cerebrovascular disorder, and respite care (statistical analysis between groups not reported). [40]

General:
The use of NSAIDs has been linked to an increased risk of myocardial infarction and stroke, and safety warnings have been issued about the use of celecoxib, etoricoxib, valdecoxib, and naproxen (see *Clinical Evidence* review on NSAIDs).

Comment: None.

QUESTION What are the effects of treatments on behavioural and psychological symptoms of dementia (Alzheimer's, Lewy body, or vascular)?

OPTION ACETYLCHOLINESTERASE INHIBITORS (DONEPEZIL, GALANTAMINE, RIVASTIGMINE) VERSUS PLACEBO IN PEOPLE WITH BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA New

Behavioural and psychological symptoms
Compared with placebo Acetylcholinesterase inhibitors (donepezil and galantamine) may be marginally more effective than placebo at improving neuropsychiatric symptoms (measured by Neuropsychiatric Inventory [NPI] scores) in

people with Alzheimer's disease and vascular dementia. We don't know whether rivastigmine is more effective than placebo at improving neuropsychiatric symptoms (measured by NPI) in people with Lewy body dementia (very low-quality evidence).

Note
Acetylcholinesterase inhibitors may be associated with adverse effects, including GI adverse effects (e.g., nausea, vomiting, diarrhoea, anorexia).

For GRADE evaluation of interventions for dementia, **see table, p 22 .**

Benefits:

Acetylcholinesterase inhibitors versus placebo:
We found two systematic reviews with different inclusion criteria which performed different analyses, [20] [24] and found three subsequent RCTs. [41] [22] [42]

The first review (search date 2005; double-blind RCTs in people with mild, moderate, or severe Alzheimer's disease) included RCTs in which treatment had been given for 6 months or longer, and at the dose recommended as optimal by the manufacturing pharmaceutical company. [20] It pooled data on acetylcholinesterase inhibitors as a group, and performed an intention-to-treat analysis with the last observation carried forwards. All the RCTs in the analysis had been published. The review found that acetylcholinesterase inhibitors significantly improved neuropsychiatric symptoms compared with placebo at 26 weeks (measured by Neuropsychiatric Inventory [NPI]: 3 RCTs [2 RCTs of donepezil; 1 RCT of galantamine]; 1005 people; WMD –2.4, 95% CI –4.1 to –0.8). [20]

The second systematic review (search date 2006) examined acetylcholinesterase inhibitors for people with behavioural and psychological (non-cognitive) symptoms of dementia, and pooled results both by individual agent and by acetylcholinesterase inhibitors as a group. [24] It included RCTs of any treatment duration, dosage, and also included unpublished RCTs. In people with Alzheimer's disease, the review found that donepezil significantly reduced neuropsychiatric symptoms compared with placebo (measured by NPI: 4 RCTs [treatment length 12–52 weeks]; 866 people; SMD –0.3, 95% CI –0.2 to –0.5). One RCT, which was an outlier in terms of treatment effect and introduced heterogeneity, was excluded from this analysis. In people with Alzheimer's disease, it found that galantamine reduced neuropsychiatric symptoms compared with placebo, although the result was of borderline significance (measured by NPI: 2 RCTs [12–21 weeks' duration]; 889 people; SMD –0.13, 95% CI 0 to –0.27; P = 0.05). The review found two RCTs of donepezil and one RCT of galantamine versus placebo in people with vascular dementia. The review found that acetylcholinesterase inhibitors significantly reduced neuropsychiatric symptoms compared with placebo in people with vascular dementia (measured by NPI: SMD –2.21, 95% CI –0.01 to –0.41; RCTs included in the analysis and absolute numbers not reported). The review found one RCT (120 people; 20 weeks' duration) of rivastigmine versus placebo in people with Lewy body dementia. It found that rivastigmine was associated with a reduction in neuropsychiatric symptoms compared with placebo, but differences between groups did not reach significance (measured by NPI: 1 RCT; 100 people; SMD –0.28, 95% CI -0.67 to +0.12). [24]

The first subsequent RCT of donepezil versus placebo (272 people with Alzheimer's disease and clinically significant agitation; 12 weeks' duration) found no significant difference between groups in neuropsychiatric symptoms as measured by the Cohen-Mansfield Agitation Inventory (CMAI) or the NPI at 12 weeks (CMAI: difference between groups in reduction in scores from baseline –0.06, 95% CI –4.35 to +4.22; P = 0.98; NPI: difference between groups in reduction in scores from baseline –0.13, 95 CI –4.06 to +3.80; P = 0.95). [41]

The second and third subsequent RCTs were designed primarily to examine the effects of acetylcholinesterase inhibitors on cognition. [22] [42] However, they also reported on neuropsychiatric symptoms. The second subsequent RCT (343 people with severe Alzheimer's disease) found no significant difference between donepezil and placebo in neuropsychiatric symptoms measured by the NPI at 24 weeks (P = 0.46). [22] The third subsequent RCT (788 people with vascular dementia) found similar changes in neuropsychiatric symptoms measured by the NPI at 26 weeks (mean change: +0.6 with galantamine *v* –1.2 with placebo; reported as no significant difference; P value not reported). [42] The second and third subsequent RCTs may not have been adequately powered to recognise a clinically important difference between groups in neuropsychiatric symptoms. [22] [42]

Harms:

Acetylcholinesterase inhibitors versus placebo:
The first review found that cholinesterase inhibitors at the usual dosage significantly increased withdrawals and other adverse effects compared with placebo (see harms of acetylcholinesterase inhibitors versus placebo for people with cognitive symptoms of dementia (donepezil, galantamine, rivastigmine), p 4 . [20] The second review found that acetylcholinesterase inhibitors in vascular

dementia significantly increased people leaving the study early due to adverse effects (NNH 10, 95% CI 8 to 15). [24] The first subsequent RCT reported that adverse effects were similar between groups (statistical analysis between groups not reported). [41] The second subsequent RCT reported that most adverse effects were rated as mild or moderate. [22] The most common adverse effects were: diarrhoea, anorexia, nausea, agitation, and vomiting (diarrhoea: 10.2% with donepezil *v* 4.2% with placebo; anorexia: 6.8% with donepezil *v* 4.2% with placebo; nausea: 6.8% with donepezil *v* 1.8% with placebo; agitation: 6.3% with donepezil *v* 6.0% with placebo; vomiting: 6.3% with donepezil *v* 2.4% with placebo; statistical analysis between groups not reported). [22] The third subsequent RCT reported most adverse effects were mild to moderate in severity. [42] Adverse effects led to treatment discontinuation in 50/396 (13%) people with galantamine and 25/390 (6%) with placebo (statistical analysis between groups not reported). [42]

Comment: Many of the studies were primarily designed to measure cognition so they included people without clinically significant behavioural or psychological symptoms of dementia. The first subsequent RCT included people with clinically significant agitation. [41]

OPTION ANTIPSYCHOTIC MEDICATIONS (HALOPERIDOL, OLANZAPINE, QUETIAPINE, RISPERIDONE) VERSUS PLACEBO IN PEOPLE WITH BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

New

Behavioural and psychological symptoms

Compared with placebo Risperidone may be more effective than placebo at reducing neuropsychiatric symptoms (measured by Neuropsychiatric Inventory [NPI] or Behavioral Pathology in Alzheimer's Disease Rating [BEHAVE-AD]) at 6 to 12 weeks in people with Alzheimer's disease, and haloperidol may be more effective than placebo at reducing aggression in people with Alzheimer's disease or vascular dementia, but not in reducing agitation. We don't know whether olanzapine is more effective than placebo at reducing neuropsychiatric symptoms (measured by Neuropsychiatric Inventory [NPI] or BEHAVE-AD) at 6 to 12 weeks in people with Alzheimer's disease, vascular dementia, or mixed dementia. We don't know whether quetiapine is more effective than placebo at reducing aggressive behaviour (measured by CMAI scores) at 26 weeks in people with Alzheimer's disease or vascular dementia. Olanzapine, risperidone, and quetiapine may be no more effective than placebo at reducing time to discontinuation of treatment for any reason in people with Alzheimer's disease and psychosis, aggression, or agitation, but olanzapine and risperidone may be more effective than placebo at reducing time to discontinuation of treatment due to lack of efficacy (not further defined) (very low-quality evidence).

Note

CAUTION: In people with dementia, antipsychotics have been associated with severe adverse events including cerebrovascular adverse events and death. Regulatory bodies have issued warnings that both conventional and atypical antipsychotics are associated with an increased risk of death in elderly people treated for dementia-related psychosis.

For GRADE evaluation of interventions for dementia, **see table, p 22 .**

Benefits:

Antipsychotics versus placebo:

We found one systematic review (search date 2006) of antipsychotics versus placebo for the treatment of people with behavioural and psychological symptoms of dementia [24] and one subsequent RCT. [43] The review did not pool data for antipsychotics as a group, but pooled data for each individual agent.

The review identified five RCTs (1862 people with Alzheimer's disease, vascular dementia, or mixed dementia; treatment duration 6–10 weeks) of olanzapine versus placebo. [24] The review found no significant difference between olanzapine and placebo in reduction of neuropsychiatric symptoms as measured by the Neuropsychiatric Inventory (NPI) at 6 to 12 weeks (measured by NPI or Behavioral Pathology in Alzheimer's Disease Rating (BEHAVE-AD): 4 RCTs, 841 people; SMD –0.09, 95% CI –0.23 to +0.05). The review identified one RCT (62 people with Alzheimer's disease or vascular dementia; treatment duration 26 weeks) which found no significant difference between quetiapine and placebo in a reduction in aggressive behaviour at 26 weeks (measured by CMAI: 1 RCT, 57 people; SMD +0.06, 95% CI –0.45 to +0.57). The review found five RCTs (1905 people with Alzheimer's disease; 10–13 weeks' duration) of risperidone. It found that risperidone significantly reduced neuropsychiatric symptoms compared with placebo at 6 to 12 weeks (measured by NPI or BEHAVE-AD: 3 RCTs, 839 people; SMD –0.3, 95% CI –0.2 to –0.5). It identified one earlier review that found five RCTs (555 people; Alzheimer's disease or vascular dementia; treatment duration 3–16 weeks) comparing haloperidol versus placebo. The review found that haloperidol significantly reduced aggression compared with placebo (3 RCTs, 489 people; SMD –0.3, 95% CI –0.1 to –0.5), but found no significant difference between groups for agitation (4 RCTs, 369 people; SMD –0.12, 95% CI –0.33 to +0.08). [24]

The subsequent RCT (421 people with Alzheimer's disease and psychosis, aggression, or agitation; symptoms severe enough to justify antipsychotics in opinion of study physicians) compared olanzapine (100 people), quetiapine (94 people), risperidone (85 people), and placebo (142 people). [43] People with a primary psychotic disorder (e.g., schizophrenia) were excluded. The primary outcome was time to discontinuation of treatment, which was to reflect the judgements of participants, carers, and clinicians with regard to efficacy, safety, and tolerability into a global measure. The RCT found no significant difference between groups in time to discontinuation of treatment for any reason (range 5–8 weeks; P = 0.52; between-group analysis). It found that olanzapine and risperidone significantly increased time to discontinuation of treatment due to lack of efficacy (outcome not further defined) compared with placebo (olanzapine [22 weeks] *v* placebo [9 weeks]; P less than 0.001; risperidone [27 weeks] *v* placebo [9 weeks]; P = 0.01). It found no significant difference between quetiapine and placebo (quetiapine [9 weeks] *v* placebo [9 weeks]; P = 0.24). [43]

Harms:

Antipsychotics versus placebo:
Antipsychotics have been associated with cerebrovascular adverse events and death in people with dementia. [44] [45] [46]

The systematic review reported that olanzapine, risperidone, and haloperidol significantly increased the risk of leaving the study early due to adverse effects (olanzapine: NNH 17, 95% CI 11 to 33; risperidone: NNH 20, 95% CI 12 to 100; haloperidol: NNH 10, 95% CI 5 to 50). [24] The review highlighted UK Committee on Safety of Medicines (CSM) advice in 2004 that risperidone or olanzapine should not be used for the treatment of behavioural symptoms of dementia, and that prescribers should carefully consider the risks of cerebrovascular events. [24] The US Food and Drug Administration (FDA) and the UK CSM issued initial warnings that olanzapine and risperidone should not be used for the treatment of behavioural symptoms of dementia. In 2008, the FDA issued a further alert that both conventional and atypical antipsychotics were associated with an increase risk of mortality in elderly people treated for dementia-related psychosis (www.fda.gov).

An alert was issued in 2007 by the FDA on the association of haloperidol with QT prolongation and Torsades de Pointes and sudden death (www.fda.gov).

One systematic review (search date 2005) [47] included in the systematic review [24] found that haloperidol significantly increased the proportion of people who had a least one extrapyramidal symptom (34/101 [34%] with haloperidol *v* 18/103 [18%] with placebo; OR 2.3, 95% CI 1.2 to 4.4). [47]

The subsequent RCT found a significant difference among groups in parkinsonism or extrapyramidal signs, gait disturbance, cognitive disturbance, psychotic symptoms, and confusion or mental state change (parkinsonism or extrapyramidal signs: 12% with olanzapine *v* 2% with quetiapine *v* 12% with risperidone *v* 1% with placebo; P less than 0.001 between groups; gait disturbance: 4% with olanzapine *v* 3% with quetiapine *v* 1% with risperidone *v* 2% with placebo; P less than 0.001 between groups; cognitive disturbance: 5% with olanzapine *v* 0% with quetiapine *v* 1% with risperidone *v* 1% with placebo; P = 0.03 between groups; psychotic symptoms: 7% with olanzapine *v* 0% with quetiapine *v* 0% with risperidone *v* 2% with placebo; P = 0.004 between groups; confusion or mental state change: 18% with olanzapine *v* 6% with quetiapine *v* 11% with risperidone *v* 5% with placebo; P = 0.03 between groups). [43] It found a significant difference among groups with regard to reasons for discontinuation due to intolerability of treatment, with higher rates in the active treatment groups (intolerability, adverse effects, or death: 24% with olanzapine *v* 16% with quetiapine *v* 18% with risperidone *v* 5% with placebo; P less than 0.001 between groups). [43]

Comment:

People with dementia and their carers should be made aware of the significant dangers of these medications before their prescription. They should not be used as first-line treatment.

OPTION BENZODIAZEPINES (DIAZEPAM, LORAZEPAM) VERSUS PLACEBO IN PEOPLE WITH BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA New

We found no direct information from RCTs about benzodiazepines (diazepam, lorazepam) in the treatment of people with behavioural and psychological symptoms of dementia.

For GRADE evaluation of interventions for dementia, see table, p 22 .

Benefits:

Benzodiazepines versus placebo:
We found one systematic review (search date 2006), which compared benzodiazepines versus placebo for the treatment of people with behavioural and psychological symptoms of dementia, which found no RCTs of sufficient quality (see comment below). [24] We found no subsequent RCTs.

Harms: **Benzodiazepines versus placebo:**
We found no RCTs. The potential harms of benzodiazepines are well described. Benzodiazepines may be associated with confusion and falls in the elderly, and there is a risk of tolerance and dependence (see *Clinical Evidence* review on generalised anxiety disorder).

Comment: The review identified one RCT (135 people with Alzheimer's disease or vascular dementia) comparing intramuscular lorazepam versus placebo with a follow-up of 24 hours, which is below the minimum period of follow-up for this *Clinical Evidence* review. [24] The review found that intramuscular lorazepam significantly reduced aggressive behaviour or agitation as measured by the Cohen-Mansfield Agitation Inventory (CMAI) at 2 hours (CMAI 2 hours after first dose; SMD –0.40, 95% CI –0.06 to –0.74). The review found no significant difference between groups in the proportion of people leaving the RCT early for any reason (RR 0.86, 95% CI 0.33 to 2.24). [24]

OPTION MEMANTINE VERSUS PLACEBO IN PEOPLE WITH BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA New

Behavioural and psychological symptoms
Compared with placebo Memantine may be marginally more effective than placebo at reducing neuropsychiatric symptoms (measured by Neuropsychiatric Inventory [NPI] scores) in people with Alzheimer's disease (very low-quality evidence).

For GRADE evaluation of interventions for dementia, see table, p 22 .

Benefits: **Memantine versus placebo:**
We found one systematic review (search date 2007), which compared memantine versus placebo for the treatment of people with behavioural and psychological symptoms of dementia, and found no subsequent RCTs. [48] The review identified six RCTs of memantine versus placebo of 24 to 28 weeks' duration, all of which were in people with Alzheimer's disease who were at least 50 years old. Three RCTs had a Jadad score of 5 and three RCTs had a score of 2, and losses to follow-up ranged from 11% to 27% between studies. [48] The review found that memantine significantly reduced neuropsychiatric symptoms as measured by the Neuropsychiatric Inventory (NPI) scale compared with placebo (1730 people, total difference in mean NPI value: –1.99, 95% CI –0.08 to –3.91: P = 0.04; ITT analysis with last observation carried forwards). [48] The review noted that studies were clinically heterogeneous, particularly with respect to disease severity and the use of concomitant treatment with acetylcholinesterase inhibitor. The review also noted that three RCTs had not been published in full, and scored 2 on the Jadad scale, and lacked adequate information on blinding, randomisation, and description of withdrawals. [48]

Harms: **Memantine versus placebo:**
The review did not report on adverse effects (see memantine versus placebo for people with cognitive symptoms of dementia, p 8). [48]

Comment: Studies were designed to measure cognition so they included people without clinically significant behavioural or psychological symptoms of dementia. Memantine appears well tolerated, but at best confers only minimal benefit on the treatment of behavioural or psychological symptoms of dementia.

OPTION NON-PHARMACOLOGICAL INTERVENTIONS (AROMATHERAPY, CBT, EXERCISE) VERSUS PLACEBO IN PEOPLE WITH BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA New

Behavioural and psychological symptoms
Aromatherapy compared with placebo Aromatherapy may be more effective than placebo at reducing agitation and neuropsychiatric symptoms (measured by CMAI and Neuropsychiatric Inventory [NPI]) in people with severe dementia (type unspecified). However, evidence was weak (very low-quality evidence).

Cognitive behavioural therapy compared with placebo We don't know whether CBT is more effective than placebo at improving neuropsychiatric symptoms (very low-quality evidence).

Exercise therapy compared with placebo or usual care We don't know whether exercise therapy is more effective than placebo or usual care at improving neuropsychiatric symptoms in people with dementia (low-quality evidence).

For GRADE evaluation of interventions for dementia, see table, p 22 .

Benefits: We found one systematic review (search date 2006) of non-pharmacological interventions versus placebo for the treatment of behavioural and psychological symptoms of dementia, [24] one systematic review of exercise versus placebo, [49] and one subsequent RCT of exercise. [50]

Aromatherapy versus placebo:
The first systematic review identified two RCTs (71 people and 21 people; all with severe dementia) of aromatherapy versus placebo. [24] One RCT (71 people) was cluster randomised, and treatment length was 2 to 4 weeks. The review found that aromatherapy significantly reduced agitation and improved neuropsychiatric symptoms compared with placebo (agitation as measured by the CMAI: WMD –11.1, 95% CI –20.0 to –2.2; neuropsychiatric symptoms as measured by the Neuropsychiatric Inventory [NPI]: WMD –15.8, 95% CI –24.4 to –7.2). The type of dementia was unspecified in both RCTs, the level of blinding was not reported in one RCT, and the time of outcome assessment was not reported. [24]

CBT versus placebo:
The review included six RCTs and several case studies of behavioural management versus placebo. [24] A meta-analysis of RCTs was not possible and the review reported each RCT narratively (absolute numbers, statistical analysis between groups, and time of outcome assessment were not reported). Three of the RCTs focused on training carers in behavioural techniques. In the first RCT (62 carers), training consisted of four individual sessions on behavioural management of aggression or discussion sessions; in the second RCT (95 couples), this comprised of "community consultants" who trained family carers a behavioural treatment protocol; in the third RCT (148 couples), training consisted of 11 sessions of behaviour management over 3 months including videotapes. In the first two RCTs, the review reported that the intervention was associated with a reduction in carer-rated aggression, although there were no significant effects on agitation in the third RCT. [24] Two RCTs focused on behavioural interventions in care homes. In one RCT, which reported a comparison of two adjacent units, one of which received "behavioural treatment" (including pleasant event scheduling) the other receiving "usual care", the review reported that the intervention was associated with a reduction in staff-reported troubling behaviour, and that both groups showed less frequency of difficult behaviour over time. [24] In the other RCT (179 people), people were allocated to receive either an activities of daily living intervention, a psychosocial activities intervention, both interventions combined, placebo, or no intervention. The review reported that no changes in disruptive behaviour were observed. [24] The remaining RCT (36 carers and people with dementia) focused on using behavioural approaches to improve sleep. The intervention included sleep hygiene education, daily waking, and increased light exposure. The review reported that the intervention was associated with a reduction in waking at night and less time awake in total. [24]

Exercise versus placebo or usual care:
The systematic review (search date 2005) found two RCTs of sufficient quality. [49] The first RCT (200 nursing-home residents; mean Mini Mental State Examination [MMSE] score 21) compared exercise training three times weekly for 30 to 45 minutes for 16 weeks versus a control of social visits of the same frequency. The review found no change in feelings of depression (assessed by mood questionnaire [not further specified]; absolute numbers and statistical analysis between groups not reported). [49] The second RCT (153 people; mean MMSE 16–17) compared aerobic/endurance activities for 30 minutes daily for 3 months versus routine care. The review found that exercise improved "mood" (assessed by mood questionnaire [not further specified]; absolute numbers and statistical analysis between groups not reported). [49] The subsequent RCT (134 people in nursing homes with mild to severe Alzheimer's disease) compared a 1-hour, twice-weekly exercise programme (including aerobic, strength, flexibility, and balance training) versus routine medical care for 1 year. It found no significant differences between groups in neuropsychiatric symptoms after 1 year (NPI total mean score: 8.3 with exercise *v* 8.9 with routine medical care; P = 0.78). [50]

Harms:

Aromatherapy versus placebo:
The review did not report on harms. [24]

CBT versus placebo:
The review did not report on harms data from the RCTs. [24] Qualitative evidence in the systematic review suggested that it is important to avoid compounding feelings of failure and humiliation where people with dementia have difficulty with interventions, activities, and games. [24]

Exercise versus placebo or usual care:
The systematic review did not report on harms. [49] The subsequent RCT found no significant difference between groups in total number of falls, fractures, or deaths (reported as not significant; P value not reported). [50] The mean number of hospital admissions per person was significantly higher in the exercise group at 6 and 12 months (6 months: 0.3 with exercise *v* 0.2 with routine care; P = 0.04; 12 months: 0.6 with exercise *v* 0.2 with routine care; P = 0.04). [50]

Comment:

CBT versus placebo:
The review also identified a series of single case studies. [24] These involved tailored behavioural interventions. Several were associated with a reduction in symptoms.

OPTION ANTIDEPRESSANTS (CLOMIPRAMINE, FLUOXETINE, IMIPRAMINE, SERTRALINE) VERSUS PLACEBO IN PEOPLE WITH BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA New

Behavioural and psychological symptoms
Compared with placebo Antidepressants (clomipramine, fluoxetine, imipramine, sertraline) may be more effective than placebo at increasing the proportion of people who respond (defined as 50% or greater reduction in standard measure of depression) and at increasing the proportion of people in remission (defined as score less than 8 on 17-item Hamilton Depression Rating Scale) in people with depression associated with Alzheimer's disease (low-quality evidence).

Note
The duration of RCTs was 6 to 12 weeks. We found no RCTs of longer duration.

For GRADE evaluation of interventions for dementia, see table, p 22 .

Benefits:

Antidepressants versus placebo:
We found one systematic review (search date 2006), which compared antidepressants versus placebo for the treatment of depression in people with Alzheimer's disease. [51] We found no subsequent RCTs. The review included double-blind RCTs using any antidepressant. It identified five RCTs in total: clomipramine (21 people); fluoxetine (41 people); imipramine (28 people); and two RCTs of sertraline (44 people; 31 people). Two RCTs had Jadad quality scores of 5; the reaming three RCTs had Jadad scores of 3. The duration of RCTs was between 6 and 12 weeks. The review found that antidepressants significantly increased the proportion of people who responded compared with placebo (response defined as a 50% or greater reduction in a standardised measure for depression: 3 RCTs [sertraline, fluoxetine]; 27/58 [47%] with antidepressants *v* 16/58 [28%] with placebo; OR 2.32, 95% CI 1.04 to 5.16). [51] It found that antidepressants significantly increased the proportion of people in remission compared with placebo (defined as a score of less than 8 on the 17-item Hamilton Depression Rating Scale: 3 RCTs [sertraline, fluoxetine, clomipramine]; 26/52 [50%] with antidepressants *v* 15/54 [20%] with placebo; OR 2.75, 95% CI 1.13 to 6.65). [51]

Harms:

Antidepressants versus placebo:
The review found no significant difference between antidepressants and placebo in overall withdrawals or withdrawals because of adverse effects (overall withdrawals: 5 RCTs, 165 people; OR 0.70, 95% CI 0.29 to 1.66; withdrawals because of adverse effects: 4 RCTs, 137 people; OR 1.41, 95% CI 0.36 to 5.54). [51] The review found no significant difference between antidepressants and placebo for cognition (mean change in Mini Mental State Examination [MMSE] scores before and after treatment: 3 RCTs [fluoxetine, sertraline, imipramine]; 114 people; WMD –0.71, 95% CI –3.20 to +1.79). [51] The review was unable to analyse individual adverse effects because only two RCTs included data on these outcomes.

Comment:

The studies included in the review are small and short term, so clinicians should be alert for adverse effects. The review concluded that more large-scale RCTs are needed to clarify the benefits, and particularly the risks of antidepressant treatment in the population of people with Alzheimer's disease. [51]

OPTION MOOD STABILISERS (CARBAMAZEPINE, SODIUM VALPROATE/VALPROIC ACID) VERSUS PLACEBO IN PEOPLE WITH BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA New

Behavioural and psychological symptoms
Compared with placebo Carbamazepine may be more effective than placebo at improving symptoms (measured by Brief Psychiatric Rating Scale [BPRS]) in people with dementia. We don't know whether sodium valproate/valproic acid is more effective than placebo at improving neuropsychiatric symptoms in people with dementia (very low-quality evidence).

For GRADE evaluation of interventions for dementia, see table, p 22 .

Benefits:

Mood stabilisers versus placebo:
We found one systematic review (search date 2007), which compared anticonvulsants versus placebo for the treatment of behavioural and psychological symptoms of dementia, and no subsequent RCTs. [52] The review did not pool data, but reported each RCT separately. The review identified one RCT (51 people; 6 weeks' treatment duration) of carbamazepine of sufficient quality. It found that carbamazepine significantly improved symptoms measured by the Brief Psychiatric Rating Scale compared with placebo (7.7-point decrease with carbamazepine *v* 0.9 with placebo; absolute numbers not reported; reported as significant difference; P value not reported). [52] The

time of assessment was not reported. [52] The review reported that the physician and pharmacist were not blinded, but did not report whether the assessment was blinded. The review found three RCTs of valproate/valproic acid of sufficient quality. The review reported that none of the three RCTs found a significant difference between groups in outcomes measured by the Brief Psychiatric Rating Scale [BPRS] or the Bech-Rafelsen Mania Scale (first RCT [56 people], % improved measured by BPRS: 68% with valproate *v* 33% with placebo; P = 0.07; second RCT [172 people] and third RCT [153 people]: absolute numbers not reported; reported as no significant difference between groups; P values not reported). [52] The time of outcome assessment was not reported. [52]

Harms:

Mood stabilisers versus placebo:
The review found that carbamazepine was associated with significantly more adverse effects than placebo (59% with carbamazepine *v* 29% with placebo; P = 0.03). [52] The most common adverse effects with carbamazepine were: falls, ataxia, drowsiness, and fever (falls: 44% with carbamazepine *v* 46% with placebo; ataxia: 33% with carbamazepine *v* not reported for placebo; drowsiness: 30% with carbamazepine *v* 33% with placebo; fever: 30% with carbamazepine *v* not reported for placebo; statistical analysis between groups not reported). One included RCT (56 people) found significantly more side effects with valproate than placebo (68% with valproate *v* 33% with placebo; P = 0.03). Another included RCT (153 people) found that, compared with placebo, valproate significantly increased diarrhoea drop in platelet count (diarrhoea: P = 0.01; drop in platelet count: P = 0.002). The remaining RCT (172 people) was discontinued early due to significantly more adverse effects in the valproate group (most often somnolence). [52] For further harms data on anticonvulsants, see *Clinical Evidence* review on Epilepsy.

Comment: None.

GLOSSARY

Music therapy A process where a therapist uses active or passive musical experiences, and the relationships that develop through them, to promote health, either in an individual or group setting.

Reminiscence therapy The encouragement of people to talk about the past in order to enable past experiences to be brought into consciousness. It relies on remote memory, which is relatively well preserved in mild to moderate dementia.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) versus placebo in people with cognitive symptoms of dementia: We found two systematic reviews (search dates 2002 and 2005) analysing the effects of acetylcholinesterase inhibitors as a group [20] [21] and one subsequent RCT, both in people with Alzheimer's disease. [22] We found one systematic review (search date 2006) examining the effects of acetylcholinesterase inhibitors as a group in people with vascular dementia. [23] We found one systematic review (search date 2006), which identified one small RCT (120 people) in people with Lewy body dementia. [24] The majority of the evidence was in people with Alzheimer's disease. We also found three systematic reviews analysing the effects of donepezil, [25] rivastigmine, [26] and galantamine [27] separately in people with Alzheimer's disease, which were added as background information. Acetylcholinesterase inhibitors categorised as Likely to be beneficial.

Ginkgo biloba versus placebo in people with cognitive symptoms of dementia: We found one systematic review (search date 2006) examining the effects of ginkgo biloba in any type of dementia or mild cognitive impairment. [28] The review noted that many included RCTs were of poor methodological quality. Ginkgo biloba categorised as Unlikely to be beneficial.

Memantine versus placebo in people with cognitive symptoms of dementia: We found one systematic review (search date 2006) in people with dementia, [29] one systematic review (search date 2004) in people with Alzheimer's disease only, [30] and one systematic review (search date 2005) in people with Alzheimer's and vascular dementia. [31] All three reviews pooled data, but employed different inclusion criteria and performed different analyses. Memantine (evidence of statistical benefit, but results of unclear clinical importance) categorised as Unknown effectiveness.

Non-pharmacological interventions (cognitive stimulation, music therapy, reminiscence) versus placebo in people with cognitive symptoms of dementia: We found one systematic review (search date 2004) of reminiscence therapy in people with dementia, which included four RCTs and pooled data. [32] The four included RCTs had important methodological weaknesses. We found one systematic review (search date 2006) on the effects of music therapy in people with dementia, which found no RCTs of sufficient quality. [33] We found one systematic review (search date 2006) of cognitive stimulation in people with dementia, which found no RCTs of sufficient quality. [24] Non-

pharmacological interventions (cognitive stimulation, music therapy, reminiscence) categorised as Unknown effectiveness.

Omega 3 (fish oil) versus placebo in people with cognitive symptoms of dementia: We found one RCT (174 people) comparing docosahexanoic acid (DHA) plus eicosapentaenoic acid (EPA) versus placebo in people with mild to moderate Alzheimer's disease and reported cognitive outcomes at 6 months. [34] We found no RCTs in people with other types of dementia. Omega 3 (fish oil) categorised as Unknown effectiveness.

Statins versus placebo in people with cognitive symptoms of dementia: We found one small RCT (71 people) comparing atorvastatin versus placebo in people with mild to moderate Alzheimer's disease and reporting cognitive outcomes at 6 and 12 months. [35] We found no RCTs in people with other types of dementia. Statins categorised as Unknown effectiveness.

NSAIDs versus placebo in people with cognitive symptoms of dementia We found one systematic review on aspirin (search date 2005) for people with vascular dementia, [36] one systematic review on ibuprofen (search date 2002) in people with Alzheimer's disease, [37] and one systematic review (search date 2004) on indometacin (indomethacin) in people with Alzheimer's disease, [38] which found no RCTs of sufficient quality. We found one RCT on the effects of naproxen in people with Alzheimer's disease that reported cognitive outcomes at 1 year, [39] and one further RCT on celecoxib in people with mild to moderate Alzheimer's disease that also reported cognitive outcomes at 1 year. [40] NSAIDS categorised as Unknown effectiveness.

Acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) versus placebo in people with behavioural and psychological symptoms of dementia: We found two systematic reviews with different inclusion criteria that performed different analyses. [20] [24] The first review (search date 2005) included people with mild, moderate, or severe Alzheimer's disease. [20] The second review (search date 2006) included people with any form of dementia. [24] We found three subsequent RCTs. [41] [22] [42] The first RCT (272 people) examined the effects of donepezil in people with Alzheimer's disease and clinically significant agitation; [41] the second RCT (343 people) examined the effects of donepezil in people with severe Alzheimer's disease; [22] and the third RCT (788 people) examined the effects of galantamine in people with vascular dementia. [42] Many of the studies were primarily designed to measure cognition so they included people without clinically significant behavioural or psychological symptoms of dementia. Acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) (evidence of marginal benefit) categorised as Likely to be beneficial.

Antipsychotic medications (haloperidol, olanzapine, quetiapine, risperidone) versus placebo in people with behavioural and psychological symptoms of dementia: We found one systematic review (search date 2006) of antipsychotics for the treatment of people with behavioural and psychological symptoms of dementia [24] and one subsequent RCT (421 people) examining the effects of olanzapine, quetiapine, risperidone, and placebo in people with Alzheimer's disease and psychosis, aggression, or agitation. [43] We also found alerts from regulatory bodies and evidence of serious harms (including cerebrovascular events and death) associated with the use of antipsychotics in this group (www.fda.gov). [24] [44] [45] [46] 'Antipsychotic medications (limited evidence of effectiveness, however, associated with severe adverse effects including cerebrovascular events and death)' categorised as Trade-off between benefits and harms.

Benzodiazepines (diazepam, lorazepam) versus placebo in people with behavioural and psychological symptoms of dementia: We found one systematic review (search date 2006) of benzodiazepines versus placebo, which found no RCTs of sufficient quality. [24] One small RCT (135 people with Alzheimer's disease or vascular dementia) included in the review comparing intramuscular lorazepam versus placebo with a follow-up of 24 hours added to comments as background information (below the minimum length of follow-up specified for this *Clinical Evidence* review). Benzodiazepines (diazepam, lorazepam) categorised as Unknown effectiveness.

Memantine versus placebo in people with behavioural and psychological symptoms of dementia We found one systematic review (search date 2007) of memantine versus placebo for the treatment of people with behavioural and psychological symptoms of dementia. [48] The review found six RCTs in people with Alzheimer's disease of 24 to 28 weeks' duration and pooled data. Memantine (evidence of marginal benefit) categorised as Likely to be beneficial.

Non-pharmacological interventions (aromatherapy, CBT, exercise) versus placebo in people with behavioural and psychological symptoms of dementia: We found one systematic review (search date 2006) of non-pharmacological interventions versus placebo for the treatment of behavioural and psychological symptoms of dementia, which found two RCTs (71 people; 21 people) of aromatherapy in people with severe dementia. [24] This systematic review also included six RCTs comparing a variety of behavioural interventions versus placebo in people with dementia. The review did not pool data. We found one further systematic review on the effects of exercise, which found two RCTs (200 people; 153 people) of sufficient quality, which did not pool data, [49] and one subsequent RCT (134 people) of exercise in people with mild to severe Alzheimer's disease. [50] Included RCTs employed a variety of interventions, and some were of poor quality. Non-pharmacological interventions (aromatherapy, cognitive behavioural therapy, exercise) categorised as Unknown effectiveness.

Antidepressants (clomipramine, fluoxetine, imipramine, sertraline) versus placebo in people with behavioural and psychological symptoms of dementia: We found one systematic review (search date 2006) of antidepressants versus placebo for the treatment of depression or anxiety in people with Alzheimer's disease which pooled data. [51] The review included five small RCTs (21–44 people), all of which had a short follow-up (6–12 weeks), and did not

report longer-term results. Antidepressants (clomipramine, fluoxetine, imipramine, sertraline) for depression categorised as Likely to be beneficial.

Mood stabilisers (carbamazepine, sodium valproate/valproic acid) versus placebo in people with behavioural and psychological symptoms of dementia: We found one systematic review (search date 2007), which compared anticonvulsants versus placebo for the treatment of behavioural and psychological symptoms of dementia and no subsequent RCTs. [52] The review did not pool data. It found one RCT (51 people) on the effects of carbamazepine of sufficient quality and found three RCTs (56 people; 172 people; 153 people) on the effects of sodium valproate of sufficient quality, one of which (172 people) had been terminated early due to adverse effects. Mood stabilisers (carbamazepine, sodium valproate/valproic acid) categorised as Unknown effectiveness.

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Disclaimer

TABLE **GRADE evaluation of interventions for dementia**

Important outcomes	Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores); behavioural and psychological symptoms; adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatments on cognitive symptoms of dementia (Alzheimer's, Lewy body, or vascular)?									
At least 11 (at least 4579) [20] [21] . [22]	Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)	Acetylcholinesterase inhibitors *v* placebo in people with Alzheimer's disease	4	0	–1	–1	0	Low	Consistency point deducted for statistical heterogeneity among RCTs. Directness point deducted for large number of withdrawals
At least 5 (at least 2097) [23]	Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)	Acetylcholinesterase inhibitors *v* placebo in people with vascular dementia	4	–1	–1	0	0	Low	Quality point deducted for weak methods (randomisation, allocation concealment). Consistency point deducted for inconsistent effects depending on outcome measure used
1 (83) [24]	Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)	Acetylcholinesterase inhibitors *v* placebo in people with Lewy body dementia	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and no ITT analysis
At least 4 (at least 1111) [28]	Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)	Ginkgo biloba *v* placebo	4	–1	–1	–2	0	Very low	Quality point deducted for weak methods. Consistency point deducted for statistical heterogeneity among RCTs and inconsistent results depending on the analysis performed. Directness points deducted for inclusion of people without dementia and for some outcomes assessing additional areas (cognition, social, mood)
At least 6 (at least 2245) [29] [30] [31]	Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)	Memantine *v* placebo	4	–2	–1	0	0	Very low	Quality points deducted for incomplete reporting of results and for inclusion of large amount of unpublished data (4 out of 6 RCTs in 1 analysis). Consistency point deducted for statistical heterogeneity among RCTs
4 (93) [32]	Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)	Reminiscence therapy *v* placebo or no treatment	4	–3	0	–2	0	Very low	Quality points deducted for sparse data, unclear inclusion criteria (type and severity of dementia), and weak methods. Consistency point deducted for short follow-up and unclear outcome measurement
1 (174) [34]	Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)	Omega 3 (fish oil) *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (71) [35]	Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)	Statins *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
2 (654) [39] [40]	Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores)	NSAIDs *v* placebo	4	0	0	–1	0	Moderate	Directness point deducted for small number of comparators (naproxen, celecoxib)
What are the effects of treatments on behavioural and psychological symptoms of dementia (Alzheimer's disease, Lewy body, or vascular)?									

Important outcomes	Cognitive symptoms and function (cognitive scores, global scores, activities of daily living scores); behavioural and psychological symptoms; adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
12 (3158) [20] [24] [41] [22] [42]	Behavioural and psychological symptoms	Acetylcholinesterase inhibitors *v* placebo	4	–1	–1	–1	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for statistical heterogeneity among RCTs and conflicting results. Directness point deducted as some studies primarily designed to measure cognition (included people without clinically significant behavioural or psychological symptoms)
15 (2647) [24] [43]	Behavioural and psychological symptoms	Antipsychotics *v* placebo	4	0	–1	–2	0	Very low	Consistency point deducted for conflicting results. Directness points deducted for subjective unclear outcome in 1 RCT and for short follow-up in most RCTs
6 (1730) [48]	Behavioural and psychological symptoms	Memantine *v* placebo	4	–3	0	–1	0	Very low	Quality points deducted for weak methods (blinding, randomisation), use of unpublished data (3 of 6 RCTs), and high rate of withdrawals. Directness point deducted for clinical heterogeneity (disease severity, co-interventions)
2 (71) [24]	Behavioural and psychological symptoms	Aromatherapy *v* placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, unclear population (type of dementia), unclear blinding, unclear time of outcome assessment
6 (unclear) [24]	Behavioural and psychological symptoms	Cognitive behavioural therapy *v* placebo	4	–1	–1	–1	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for inconsistent results between RCTs. Directness point deducted for subjective outcomes
3 (487) [49] [50]	Behavioural and psychological symptoms	Exercise *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for unclear outcome assessment
At least 3 (116) [51]	Behavioural and psychological symptoms	Antidepressants (clomipramine, fluoxetine, imipramine, sertraline) *v* placebo	4	–1	0	–1	0	Low	Quality points deducted for sparse data. Directness point deducted for short follow-up (6–12 weeks)
4 (432) [52]	Behavioural and psychological symptoms	Mood stabilisers (carbamazepine, sodium valproate/valproic acid) *v* placebo	4	–3	0	0	0	Very low	Quality points deducted for incomplete reporting of results, early termination of 1 RCT, and unclear blinding

Type of evidence: 4 = RCT Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio